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Re:	Appellants:	Thomas M. DiMauro, Mohamed Attawia, Hassan Serhan, Martin A. Reynolds, Melissa Grace, Sudhakar Kadiyala, David Urbahns, Scott Bruder, Gregory Collins, Laura J. Brown, Jeff Geesin, Pamela L. Plouhar, Catherine Smith and John Siekierka
	Application No.:	10/630,227 Filed :June 30, 2003
	Confirmation No.:	8291
	Title:	Trans-Capsular Administration of High Specificity Cytokine Inhibitors Into Orthopedic Joints
	Docket No.:	3518.1015-000

Sir:

Transmitted herewith is an Amended Appeal Brief for filing in the subject application. The Amended Appeal Brief is filed pursuant to the Notification of Non-Compliant Appeal Brief mailed from the U.S. Patent and Trademark Office on October 1, 2007.

1. ☒ Appellants hereby petition to extend the time for filing an Amended Appeal Brief for 1 month from November 1, 2007 to December 1, 2007.

2. ☐ A [ ] month extension of time to extend the time for filing an Appeal Brief from [ ] to [ ] was filed on [ ] with payment of a $[ ] fee.

   ☐ Appellant hereby petitions for an additional [ ] month extension of time for filing an Appeal Brief from [ ] to [ ].

3. ☐ A Request for Oral Hearing before the Board of Patent Appeals and Interferences is being filed concurrently herewith.

4. Fees are submitted for the following:

☒	Extension of Time for 1 month		$120.00
☐	Additional Extension of Time:		
	Fee for Extension ([ ] mo.)	$_____	
	Less fee paid ([ ] mo.)	$_____	
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☐	Appeal Brief		$_____
☐	Other_____		$_____
		TOTAL	$120.00

5. The method of payment for the total fees is as follows:

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☒ Please charge Deposit Account No. 08-0380 in the amount of $120.00.

Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380. A copy of this letter is enclosed for accounting purposes.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Deirdre E. Sanders

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Dated: December 3, 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Thomas M. DiMauro, Mohamed Attawia, Hassan Serhan, Martin A. Reynolds, Melissa Grace, Sudhakar Kadiyala, David Urbahns, Scott Bruder, Gregory Collins, Laura J. Brown, Jeff Geesin, Pamela L. Plouhar, Catherine Smith and John Siekierka

Application No.:	10/630,227	Group:	1647
Filed:	July 30, 2003	Examiner:	Shulamith H. Shafer

Confirmation No.: 8291

For: TRANS-CAPSULAR ADMINISTRATION OF HIGH SPECIFICITY CYTOKINE INHIBITORS INTO ORTHOPEDIC JOINTS

CERTIFICATE OF MAILING OR TRANSMISSION

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AMENDED APPEAL BRIEF

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Commissioner for Patents
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Alexandria, VA 22313-1450

Sir:

This Amended Appeal Brief is submitted pursuant to the Notice of Appeal received in the U.S. Patent and Trademark Office on November 30, 2006, and in support of the appeal from the rejections set forth in the Office Action mailed on June 27, 2006 and in the Notice of Panel Decision from the Pre-Appeal Brief Review mailed January 25, 2007, and further in response to the Notification of Non-Compliant Appeal Brief mailed from the U.S. Patent and Trademark Office on October 1, 2007. The Appeal Brief filed May 30, 2007 is considered to be non-compliant because it did not address rejections to Claims 50 and 55 cited in the Office Action mailed January 25, 2007. Sections C and E have been amended in this Amended Appeal Brief

for compliance in accordance with the Notification of Non-Compliant Appeal Brief. The exhibits listed herein were submitted with the Appeal Brief filed on May 30, 2007. The Examiner has twice rejected Claims 1, 2, 34, 36-43, 45-51, 53-58, 60-61 and 63-65. The authorization for charging the fee to Deposit Account No. 08-0380 for filing a brief in support of an appeal was enclosed with the mailing of the Appeal Brief on May 30, 2007.

An extension of time to respond to the Notification of Non-Compliant Appeal Brief is respectfully requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently with this Amended Appeal Brief.

I. REAL PARTY IN INTEREST

The real party in interest is DePuy Spine, Inc., a corporation existing under the laws of the State of Ohio, and having a usual place of business at 325 Paramount Drive, Raynham, MA 02767. DePuy Spine, Inc., is the Assignee of the entire right, title and interest in the subject application, by virtue of an Assignment recorded on at Reel 014950, Frames 0123-0150 and at Reel 015160, Frames 0123-0127.

II. RELATED APPEALS AND INTERFERENCES

Appellants, the undersigned Attorney and the Assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

A listing of appealed claims appears in the Claims Appendix of this Brief. Claims 1, 2, 34, 36-43, 45-51, 53-58, 60-65 and 89-92 are pending. Claims 14, 44 and 59 were canceled. Claims 3-13, 15-33, 35, 52 and 66-88 were withdrawn.

Claims 1, 2, 34, 36-43, 45-51, 53-58, 60-61 and 63-65 have been twice rejected. Claims 84-92 are pending but have not been twice rejected. Claim 62 was incorrectly treated as withdrawn in the first Office Action and was rejected in the second Office Action. Therefore, it is pending but has not been twice rejected. Thus, the claims under appeal are as follows: Claims 1, 2, 34, 36-43, 45-51, 53-58 and 60-61 and 63-65.

IV. STATUS OF AMENDMENTS

In an Amendment filed on April 4, 2006, Claims 1, 34, 38, 48, 51, 55, 63 and 65 were amended and Claims 84-92 were added. No amendments have been filed subsequent to the Office Action mailed June 27, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis. As taught in Appellants' specification, direct administration of the inhibitor of TNF-α synthesis trans-capsularly is advantageous over systemic treatment. Such advantages include, for example, arresting the inflammation process commencing within the joint and the degeneration of the hyaline cartilage, preventing intracapsular nerve irritation and pain, increasing the half life of the inhibitor of TNF-α synthesis in the capsule, reducing unwanted side effects and permitting combination with other therapeutic agents without reducing their effectiveness (see the specification, for example at page 7, line 19 to page 9, line 25).

There is one independent claim, Claim 1. Appellants' invention is a method of treating an inflamed orthopedic joint, said joint comprising i) opposing hyaline cartilage articular surfaces, ii) a peripheral collagenous capsule defining a central joint space and iii) synovial fluid contained within the joint space, comprising trans-capsularly administering into the joint space a formulation comprising an effective amount of an inhibitor of TNF-α synthesis such that the inflamed orthopedic joint is treated (Claim 1). In one particular aspect, the orthopedic joint is a knee joint (Claim 2). (see the specification, for example at page 11, line 23 to page 12, line 14).

In one particular aspect (Claim 51), the inhibitor of TNF-α synthesis therapeutically inhibits the production of a cytokine (see the specification, for example at page 14, lines 17-18). In another particular aspect (Claim 34), the administered formulation further comprises at least one growth factor (see the specification, for example at page 32, line 11 to page 33, line 2). In another particular aspect (Claim 49), the administered formulation further comprises a growth factor present in an amount effective to repair joint tissue. In another particular aspect (Claim 50), the growth factor is provided by platelet concentrate (see the specification, for example, at page 32,line 1 to page 33, line 10). In another particular aspect (Claim 54), the administered formulation includes a viscosupplement (see the specification, for example at page 23, line 22 to page 24, line 5).

In another particular aspect (Claim 37), the formulation is administered in an amount of less than 1 cc (see the specification, for example at page 22, line 28 to page 23, line 5). In another particular aspect (Claim 38), the inhibitor of TNF-α synthesis is present in the formulation in an amount of at least 100 mg/ml (see the specification, for example at page 23, lines 15-16). In another particular aspect (Claim 48), the inhibitor of TNF-α synthesis is present in the formulation in a maximum amount of 0.5 mg (see the specification, for example at page 22, line 10 to page 23, line 21).

In another particular aspect (Claim 39), the administered formulation further comprises a sustained release device. In another particular aspect (Claim 40), the sustained delivery device comprises a hydrogel. In another particular aspect (Claim 41), the sustained delivery device provides controlled release. In another particular aspect (Claim 42), the sustained delivery device provides continuous release. In another particular aspect (Claim 43), the sustained delivery device provides intermittent release. In another particular aspect (Claim 45), the sustained delivery device comprises microspheres having a plurality of degradation rates. In another particular aspect (Claim 46), the sustained delivery device comprises an inflammatory-responsive delivery system (see the specification, for example at page 24, line 21 to page 25, line 17).

In another particular aspect (Claim 63), the inhibitor of TNF-α synthesis is predominantly released from the formulation by diffusion through a sustained delivery device. In another particular aspect (Claim 64), the sustained delivery device is a polymer. In another particular aspect (Claim 65), the inhibitor of TNF-α synthesis is predominantly released from the formulation by biodegradation of a sustained delivery device (see the specification, for example at page 24, line 21 to page 25, line 17).

In another particular aspect (Claim 47), the formulation is provided closely adjacent to the outer wall of the capsule (see the specification, for example at page 13, lines 1-2). In another particular aspect (Claim 60), the formulation is provided in a patch attached to an outer wall of the capsule (see the specification, for example at page 12, lines 17-29). In another particular aspect (Claim 61), the administration comprises providing the formulation in a depot at a location closely adjacent an outer wall of the capsule (see the specification, for example at page 13, lines 1-2). In another particular aspect (Claim 36), the administered formulation further

comprises a liposomal delivery system (see the specification, for example at page 25, line 21 to page 26, line 12).

In another particular aspect (Claim 53), the formulation is injected into the synovial fluid (see the specification, for example at page 29, lines 13-17). In another particular aspect (Claim 55), a portion of the synovial fluid is removed prior to administration of the inhibitor of TNF-α synthesis (see the specification, for example at page 29, lines 23-25). In another particular aspect (Claim 56), the formulation is administered through a needle (see the specification, for example at page 29, lines 18-22). In another particular aspect (Claim 57), the formulation is administered through a drug pump (see the specification, for example at page 30, line 4). In another particular aspect (Claim 58), the formulation is administered in a volume of between 0.03 ml and 0.3 ml. (see the specification, for example at page 29, lines 5-11).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether Claims 1, 2, 34, 37, 47, 49, 51, 54 and 56 are properly rejected under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics, 140*:125-127 (2002) in view of Dunn (EP 1 153 606).

B. Whether Claims 36, 39-43, 45, 58, 60, 61, 63-65 are properly rejected under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics, 140*:125-127 (2002) in view of Pike *et al.* (US Publication No. 20030134792).

C. Whether Claim 50 is properly rejected under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics, 140*:125-127 (2002) in view of Dunn (EP 1 153 606) and Molloy *et al. Sports Med., 33*:381-394 (2003).

D. Whether Claims 1, 53 and 57 are properly rejected under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics, 140*:125-127 (2002) in view of Smith *et al.* (U.S. Publication No. 20020169162).

E. Whether Claim 55 is properly rejected under 35 U.S.C. § 103(a) as being obvious over Lehman *et al.*, *The Journal of Pediatrics, 140*:125-127 (2002) in view of Dunn (EP 1 153 606) and Cardone *et al.*, *American Family Physician, 67*:2147-2152 (2003).

F. Whether Claim 1 is properly rejected under 35 U.S.C. § 103(a) as being obvious over Dunn (EP 1 153 606) in view of Braun and Sieper, *Expert Opin. Biol. Ther.* 3(1): 141-168 (2003).

G. Whether Claims 38 and 48 are properly rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

H. Whether Claims 38 and 48 are properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

I. Whether Claim 46 is properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

J. Whether Claim 49 is properly rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

K. Whether Claim 49 is properly rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

VII. ARGUMENT

A. CLAIMS 1, 2, 34, 37, 47, 49, 51, 54 AND 56 ARE NOT PROPERLY REJECTED UNDER 35 U.S.C. §103(a) AS BEING OBVIOUS OVER LEHMAN *ET AL., THE JOURNAL OF PEDIATRICS, 140*:125-127 (2002) IN VIEW OF DUNN (EP 1 153 606).

Appellants' independent claim, Claim 1, is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. Claims 2, 34, 37, 47, 49, 51, 54 and 56 depend upon Claim 1, and, therefore, contain the same limitation.

The Examiner states that "[i]t would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the formulation comprising thalidomide taught by Lehman et al. using the administration route taught by Dunn". (see page 7 of Office Action mailed January 4, 2006 (First Office Action) and page 13 of Office Action mailed June 27, 2006 (Second Office Action)).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in some knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of

success must be found in the prior art and not based in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *Manual of Patent Examining Procedure* § 706.02(j).

Appellants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis. As taught in Appellants' specification, direct administration of the inhibitor of TNF-α synthesis trans-capsularly is advantageous over systemic treatment. Such advantages include, for example, arresting the inflammation process begun within the joint and the degeneration of the hyaline cartilage, preventing intracapsular nerve irritation, increasing the half life of the inhibitor of TNF-α synthesis in the capsule and reducing unwanted side effects (see the specification, for example at page 8, line 10 to page 10, line 5).

Lehman *et al.* teaches that two children with systemic onset juvenile rheumatoid arthritis were systemically treated with etanercept (ENBREL®) and thalidomide. The treatment with etanercept was unsuccessful. The treatment with thalidomide demonstrated improvements in arthritis manifestations and laboratory parameters. However, Lehman *et al.* teaches that thalidomide has been shown to have both stimulatory and inhibitory effects on TNF-α activity, and notes that it may increase TNF-α production under some circumstances (see Lehman *et al.* at page 126, column 3). Further, Lehman *et al.* cites reference number fourteen (14), Gori *et al.*, "Tumor Necrosis Factor-α Increased Production During Thalidomide Treatment in Patients with Tuberculosis and Human Immunodeficiency Virus Coinfection", *J. Infect. Dis. 182*:639-640 (2000). Gori *et al.* states that reported data suggest that thalidomide is *not* a systemic TNF-α inhibitor. In fact, Gori *et al.* reported a progressive increase in TNF-α production following thalidomide treatment, concluding "we confirm that thalidomide did not reduce TNF-α levels...." (page 639). Further, Gori *et al.* states that, in light of these results, they suggest "extreme caution" in undertaking studies that support clinical use of thalidomide. *Id.* The Examiner states that the relevance of Gori is unclear because Gori is directed to treating a different population of patients. However, Lehman *et al.*'s citation of Gori indicates that Lehman *et al.* believes Gori's research is relevant to Lehman *et al.*'s findings.

The Examiner states that Appellants' specification teaches that thalidomide is among the compounds which prevent and/or inhibit TNF synthesis. However, what the specification actually discloses is that TNF antagonists include "compounds which prevent and/or inhibit TNF

synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g, pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers...." (page 15, lines 21-24). One of skill in the art would not conclude that thalidomide is an inhibitor of TNF-α synthesis, as recited in the claims.

Therefore, Lehman *et al.* does not teach or suggest administration via trans-capsular injection, and does not teach or suggest treating an inflamed orthopedic joint with an inhibitor of TNF-α synthesis. In fact, Lehman *et al.* teaches away from administration of an inhibitor of TNF-α synthesis in favor of a substance known to have at least some stimulatory effects on TNF-α activity (thalidomide). A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984), MPEP § 2142.02 (VI). Because thalidomide can increase TNF-α synthesis, Lehman *et al.* does not inherently teach treatment with an inhibitor of TNF-α synthesis. Moreover, even if it did, it does not teach or suggest local or trans-capsular administration. Thus, Lehman *et al.* does not describe or suggest Appellants' invention, and does not provide a reasonable expectation of successfully treating an inflamed orthopedic joint by trans-capsularly administering into the joint space an inhibitor of TNF-α synthesis.

Dunn teaches treating an inflamed joint by injecting growth hormone and buffer solution into the joint space. (See Dunn, column 3, paragraph 0009 and 0011). According to Dunn, the hormone is injected into the joint space and not directly into the bone, and in this manner it may flow over the entire joint surface and react with the vascular units at the bone-cartilage interface, and it may be absorbed into the bloodstream resulting in systemic effects, such as stimulation of production of bone marrow outside the joint. (See Dunn, column 7, paragraph 0027). The purpose of injection of the growth factor into the joint is to stimulate the articular growth plate at the joint surface. (See Dunn column 5, paragraph 0021 to column 6, paragraph 0023).

Dunn further discloses that, as a "preliminary" step, agents such as anti-kinases, growth factors and anti-cytokines including ENBREL® can be injected or otherwise applied to the joint prior to, or simultaneously with, the step of injecting a growth hormone and buffer solution into the joint space. (See Dunn abstract; column 8, paragraph 0030; and column 9, paragraph 0031). According to Dunn, the presence of these agents has the effect of "quieting" the joint due to the reduction or removal of the irritating activity of certain agents, e.g., TNF, which might impede or

impair the responsiveness of the joint to subsequent treatment with growth hormone for inflammation. ENBREL® does not inhibit TNF-α synthesis. Thus, Dunn does not describe or suggest Appellants' methods of administration of an inhibitor of TNF-α synthesis.

Even if thalidomide were inherently an inhibitor of TNF-α synthesis, one of skill in the art would not be motivated to substitute an inhibitor of TNF-α synthesis for the growth factor in Dunn to *trans-capsularly* administer an inhibitor of TNF-α synthesis on the basis of Lehman *et al.*'s teachings of *systemic* administration of thalidomide.

Further at the time of Appellants' invention, one of skill in the art would not have been motivated to locally administer any inhibitor of TNF-α synthesis. The state of the art was not to administer such compounds trans-capsularly. For example, as noted in Appellants' specification, at least one published application teaches in its examples that TNF inhibitors are to be administered through systemic pathways. Appellants' specification discloses that, in particular, a cited published application teaches that "the major contribution of TNF-alpha may be derived from recruited, aggregated and maybe even extravasated leukocytes, and that successful pharmacologic block may be achieved only by systemic treatment" (Appellants' specification, page 4, lines 8-17).

Thus, one of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Dunn with any reasonable expectation of success in treating an inflamed orthopedic joint by trans-capsularly administering an inhibitor of TNF-α synthesis, as claimed by Appellants. None of the Examiner's cited references alone or in combination teach or suggest the claimed invention, and the claimed invention is not obvious.

B. CLAIMS 36, 39-43, 45, 58, 60, 61, 63-65 ARE NOT PROPERLY REJECTED UNDER 35 U.S.C. § 103(a) AS BEING OBVIOUS OVER LEHMAN *ET AL., THE JOURNAL OF PEDIATRICS, 140*:125-127 (2002) IN VIEW OF PIKE *ET AL.* (US PUBLICATION NO. 20030134792).

Claims 36, 39-43, 45, 58, 60, 61 and 63-65 recite various aspects of administration. They depend upon Claim 1, and, therefore, are also directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. The Examiner states that these claims are obvious over Lehman *et al.* in view of Pike *et al.* However,

none of the Examiner's cited references alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis.

As discussed above, Lehman *et al.* does not teach or suggest administration via trans-capsular injection of an inflamed orthopedic joint with an inhibitor of TNF-α synthesis, nor does it teach the different aspects of administration disclosed in the rejected claims. Pike *et al.* discloses the treatment of articular cartilage disorders by administering IGF-1, a growth factor, to preserve existing cartilage tissues or stimulate regeneration of cartilage. Such treatment includes administering IGF-1 by, for example, intra-articular injection. Although Pike *et al.* teaches that additional agents such as antibodies and anti-inflammatory agents can be included in its composition, Pike *et al.* does not teach or suggest administering an inhibitor of TNF-α synthesis, or any anti-cytokine agent. Thus, neither Lehman *et al.* nor Pike *et al.* describe or suggest Appellants' invention, and do not provide a reasonable expectation of treating an inflamed orthopedic joint by trans-capsularly administering an inhibitor of TNF-α synthesis.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based on Appellant's disclosure. Thus, for these reasons and the reasons discussed above, one of skill in the art would not be motivated to substitute an inhibitor of TNF-α synthesis for the growth factor in Pike *et al.* on the basis of Lehman *et al.*'s teachings of systemic administration of thalidomide. One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Pike *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint with an inhibitor of TNF-α synthesis, as claimed by Appellants. None of the Examiner's cited references alone or in combination teach or suggest the claimed invention, and the claimed invention is not obvious.

C. CLAIM 50 IS NOT PROPERLY REJECTED UNDER 35 U.S.C. § 103(a) AS BEING OBVIOUS OVER LEHMAN *ET AL., THE JOURNAL OF PEDIATRICS, 140*:125-127 (2002) IN VIEW OF DUNN (EP 1 153 606), AND MOLLOY *ET AL., SPORTS MED., 33*:381-394 (2003).

As noted above, Appellants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising an inhibitor of TNF-α synthesis. Claim 50 is directed to the method wherein the formulation further comprises a growth factor provided by platelet concentrate. The Examiner states that this claim is obvious over Lehman *et al.* in view of Dunn and Molloy *et al* (second Office Action, dated June 27, 2006). However, the Examiner's cited references in combination do not teach or suggest the claimed invention.

For the reasons discussed above, Lehman *et al.*, Dunn and Molloy *et al.* in combination do not teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. Specifically, Lehman *et al.* teach systemic administration of thalidomide, and teaches away from local treatment with a inhibitor of TNF-α synthesis. Lehman *et al.* do not teach such a formulation that further comprises a growth factor provided by platelet concentrate. Dunn teaches treating an inflamed joint by injecting growth hormone and buffer solution into the joint space. Molloy *et al.* teaches that growth factors play a role in tendon healing.

One of skill in the art would not be motivated to substitute the thalidomide of Lehman *et al.* into the method of Dunn to arrive at the invention claimed in Claim 50. The state of the art was not local administration into a joint of an inhibitor of TNF-α synthesis, even though there was a long felt need for more effective treatment of joint inflammation. Thus, one of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.*, Dunn and Molloy *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint by trans-capsularly administering an inhibitor of TNF-α synthesis and a growth factor provided by platelet concentrate. The claimed invention is not obvious.

D. CLAIMS 1, 53 AND 57 UNDER 35 U.S.C. § 103(a) ARE NOT PROPERLY REJECTED UNDER 35 U.S.C. § 103(a) AS BEING OBVIOUS OVER LEHMAN *ET AL., THE JOURNAL OF PEDIATRICS, 140*:125-127 (2002) IN VIEW OF SMITH *ET AL.* (U.S. PUBLICATION NO. 20020169162).

As noted above, Appellants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising an inhibitor of TNF-α synthesis. Claim 53 is directed to the method of Claim 1, wherein the formulation is injected into the synovial fluid. Claim 57 is directed to the method of Claim 1, wherein the formulation is administered through a drug pump.

The Examiner states that these claims are obvious over Lehman *et al.* in view of Smith *et al.* (first and second Office Actions). However, none of the Examiner's cited references alone or in combination teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. As discussed above, Lehman *et al.* teaches systemic administration of thalidomide. Lehman *et al.* does not teach or suggest trans-capsularly administering an inhibitor of TNF-α synthesis in the synovial fluid-containing portion of the joint, or administering an inhibitor of TNF-α synthesis through a drug pump.

Smith *et al.* teaches a sustained release device which may be surgically implanted intraarticularly, *i.e.*, within the synovial joint. (See Smith *et al.* at paragraph 0046). According to Smith *et al.*, the sustained release device is capable of releasing drugs or compounds over an extended period of time in a controlled fashion, as opposed to repeated injections (See Smith *et al.* at paragraphs 0012 and 0047). Smith *et al.* teaches that the compounds that can be administered via the sustained release device include glucocorticoids, anti-inflammatories such as dexamethasone, fluocinolone, cortisone, prednisolone, flumetholone, and derivatives thereof; non-steroidal anti-inflammatory drugs and cyclosporines. (See Smith at paragraph 0043). Smith *et al.* does not teach or suggest administering an inhibitor of TNF-α synthesis. Thus, neither Lehman *et al.* nor Smith *et al.* describes or suggests Appellants' invention. One of skill in the art would not be motivated by Lehman *et al.*'s systemic administration of thalidomide to substitute an inhibitor of TNF-α synthesis into Smith *et al.*'s methods.

One of ordinary skill in the art would not be motivated to combine the teachings of Lehman *et al.* and Smith *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint, by trans-capsular administration of an inhibitor of TNF-α synthesis either by

synovial fluid injection or by drug pump as claimed by Appellants. Thus, none of the references cited by the Examiner alone or in combination teach or suggest the claimed invention, and the claimed invention is not obvious.

E. CLAIM 55 IS NOT PROPERLY REJECTED UNDER 35 U.S.C. § 103(a) AS BEING OBVIOUS OVER LEHMAN *ET AL., THE JOURNAL OF PEDIATRICS, 140*:125-127 (2002) IN VIEW OF DUNN (EP 1 153 606) AND CARDONE *ET AL., AMERICAN FAMILY PHYSICIAN, 67*:2147-2152 (2003).

Claim 55 is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising inhibitor of TNF-α synthesis wherein a portion of the synovial fluid is removed prior to administration of the inhibitor of TNF-α synthesis. The Examiner states that this claim is obvious over Lehman *et al.* and Dunn in view of Cardone *et al.* (second Office Action) However, the references cited by the Examiner do not teach or suggest the claimed invention.

For the reasons discussed above, Lehman *et al.*, Dunn and Cardone *et al* in combination do not teach or suggest treating an inflamed orthopedic joint comprising trans-capsularly administering an inhibitor of TNF-α synthesis. Specifically, Lehman *et al.* teach systemic administration of thalidomide, and teaches away from local treatment with a inhibitor of TNF-α synthesis. Lehman *et al.* do not teach such a formulation that further comprises a growth factor provided by platelet concentrate. Dunn teaches treating an inflamed joint by injecting growth hormone and buffer solution into the joint space. Cardone *et al.* teaches injection procedures for administering corticosteroids into the hip and knee joints as diagnostic and therapeutic tools. In addition, Cardone *et al.* teaches aspiration procedures for the knee for the purpose of diagnosing an unexplained effusion and to relieve discomfort caused by the effusion. Cardone *et al.* does not teach or suggest removing a portion of the synovial fluid prior to trans-capsular administration of an inhibitor of TNF-α synthesis.

One of skill in the art would not be motivated to substitute the thalidomide of Lehman *et al.* into the method of Dunn to arrive at the invention claimed in Claim 55. The state of the art was not local administration into a joint of an inhibitor of TNF-α synthesis, even though there was a long felt need for more effective treatment of joint inflammation. Thus, one of ordinary

skill in the art would not be motivated to combine the teachings of Lehman *et al.*, Dunn and Molloy *et al.* with any reasonable expectation of success in treating an inflamed orthopedic joint by trans-capsularly administering a formulation comprising inhibitor of TNF-α synthesis wherein a portion of the synovial fluid is removed prior to administration of the inhibitor of TNF-α synthesis The claimed invention is not obvious.

F. CLAIM 1 IS NOT PROPERLY REJECTED UNDER 35 U.S.C. § 103(a) AS BEING OBVIOUS OVER DUNN (EP 1 153 606) IN VIEW OF BRAUN AND SIEPER, *EXPERT OPIN. BIOL. THER.* 3(1): 141-168 (2003).

As noted above, Appellants' invention is directed to a method of treating an inflamed orthopedic joint comprising trans-capsularly administering a formulation comprising an inhibitor of TNF-α synthesis.

As discussed in detail above, Dunn does not describe trans-capsular administration of an inhibitor of TNF-α synthesis, and does not teach the invention of Claim 1. Braun teaches use of infliximab, a chimeric anti-TNF antibody, to treat rheumatoid arthritis by single *intravenous* (i.e., systemic) infusions. It does not teach or suggest trans-capsular administration into a joint space, nor does it teach any potential value of any local administration. One of skill in the art would not have been motivated to substitute infliximab in the methods of Braun with a reasonable expectation of success. The motivation to combine must come from the references themselves and not from the benefit of hindsight based on teachings in the Appellants' specification. Thus, the claimed invention is not obvious.

G. CLAIMS 38 AND 48 ARE NOT PROPERLY REJECTED UNDER 35 U.S.C. §112, SECOND PARAGRAPH AS BEING INDEFINITE.

Claim 38 is directed to the method of Claim 1, wherein the inhibitor of TNF-α synthesis is present in the formulation in an amount of at least 100 mg/ml. Claim 48 is directed to the method of Claim 1, wherein the inhibitor of TNF-α synthesis is present in the formulation in a maximum amount of 0.5 mg. The Examiner has rejected these claims as indefinite, stating that "[i]n the absence of a specific recited structure, the recitation of a specific dosage is meaningless." (first Office Action).

With regard to the definiteness requirement of 35 U.S.C. § 112, second paragraph, the Examiner's focus during examination of the claims for compliance with the requirement for definiteness is "whether the claim meets the threshold requirements of clarity and precision...." See *Manual of Patent Examining Procedure* (MPEP) §2173.02.

> When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the manner of terms should be permitted even though the claim language is not as precise as the examiner might desire.

Id. (emphasis in original)

Claims 38 and 48 recite administration of particular amounts of "an inhibitor of TNF-α synthesis." Since none of the other claims reciting "an inhibitor of TNF-α synthesis" are rejected as indefinite, it appears that the rejection is directed to the use of amounts. Definiteness of claim language must be analyzed not in a vacuum, but in light of the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. *Id.* One of ordinary skill in the art should understand what is meant by amounts of such inhibitors in units such as "mg/ml" and of "mg". Thus, it would be very straightforward for one of ordinary skill in the art to understand what is meant by an inhibitor of TNF-α synthesis "present in the formulation in an amount of at least 100 mg/ml" and "present in the formulation in a maximum amount of 0.5 mg" (see, for example, the specification at page 22, line 10 to page 23, line 21). Thus, each claim "apprises one of ordinary skill in the art of its scope and, therefore, serves its notice function...." and "defines the patentable subject matter with reasonable degree of particularity and distinctness." *Id.* The claims are definite.

H. CLAIMS 38 AND 48 ARE NOT PROPERLY REJECTED UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, AS FAILING TO COMPLY WITH THE ENABLEMENT REQUIREMENT.

The Examiner has also rejected Claims 38 and 48 as not enabled, stating "[i]n the absence of a specific recited structure the skilled artisan is unable to make the recited compound" (first

Office Action). As indicated above, Claims 38 and 48 recite administration of particular amounts of an inhibitor of TNF-α synthesis. The claims do not require the artisan to make the compounds; they merely require the artisan to measure them. Otherwise, these claims do not differ from Claim 1, which is not rejected for enablement. The level of skill is the art is high. Inhibitors of TNF-α synthesis are well-known and available in the art, as are procedures to measure them. One of skill in the art could easily determine how to measure an inhibitor of TNF-α synthesis in a formulation in an amount of at least 100 mg/ml or in a formulation in a maximum amount of 0.5 mg without undue experimentation. (see, for example, the specification at page 22, line 10 to page 23, line 21). The claims are enabled.

I. CLAIM 46 IS NOT PROPERLY REJECTED UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, AS FAILING TO COMPLY WITH THE ENABLEMENT REQUIREMENT.

Claim 46 recites "wherein the sustained release device comprises an inflammatory-responsive delivery system." The Examiner rejects this claim, stating that "[t]he specification provides no guidance and/or direction or working examples of a sustained release device which could deliver a formulation comprising an effective amount of an inhibitor of TNF-α synthesis." In addition, the Examiner states that LaVan *et al.* discloses that there are stability problems with *in vivo* glucose sensors.

Although LaVan *et al.* discloses that there are stability problems with *in vivo* glucose sensors, LaVan *et al.* does not disclose any such problems with a sustained release device that comprises an inflammatory-responsive delivery system. In fact, Pike *et al.* (US Publication No. 20030134792), which was cited by the Examiner in §103(a) rejections, states at paragraph 0053 that a sustained release device comprising inflammatory-responsive delivery systems is "well known in the art," and can be used to administer a therapeutically effective dose of an agent directly at the site. The Examiner states that LaVan *et al.* indicates that "smart" delivery devices require more safety and efficacy testing before clinical use, and "one could logically conclude that these systems were not yet reduced to practice." (second Office Action). However, enablement does not require reduction to practice or establishment of a particular degree of safety or efficacy. The proper standard is whether one of skill in the art can make or use the

claimed invention without undue experimentation. The teachings in the specification, combined with what was known in the art, establish that this standard is met. Thus, Claim 46 is enabled.

J. CLAIM 49 IS NOT PROPERLY REJECTED UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, AS FAILING TO COMPLY WITH THE ENABLEMENT REQUIREMENT.

Claim 49 recites "wherein the formulation further comprises a growth factor present in an amount effective to repair joint tissue." The Examiner states that Claim 49 is not enabled because the specification fails to teach the skilled artisan how to use the factors recited without undue experimentation to determine whether a given protein would be useful in the claimed methods and what the dosage would be (second Office Action). The specification discusses the factors in detail (e.g., page 32, line 11-page 33, line 2). The level of skill in the relevant art is high, and therapeutic administration of growth factors was well-known at the time of the invention (see, for example, Dunn *et al.* and Pike *et al.* above). A skilled practitioner could easily determine whether an inflamed knee joint is being treated, and how to determine appropriate dosage of known factors for such treatment, with only routine experimentation, the claim is enabled.

K. CLAIM 49 IS NOT PROPERLY REJECTED UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, AS FAILING TO COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT.

Claim 49 recites "wherein the formulation further comprises a growth factor present in an amount effective to repair joint tissue." The Examiner has rejected this claim as failing to meet these written description requirement on the grounds that the specification does not "clearly allow persons of ordinary skill in the art to recognize [he or she] invented what is now claimed [with regard to "growth factors]" (second Office Action).

As noted above, at the time of the invention, therapeutic administration of growth factors may was well known. As noted by the Examiner, the specification lists a myriad of growth factors that may be used in the invention (see, e.g., page 32, line 11-page 33, line 2). As further

noted by the Examiner, the skilled artisan would be aware of a number of different compounds which would be classified under the heading "growth factors". Appellants are not required to put into a specification what is well known. Clearly, the claimed subject matter is described in the specification in a manner which does demonstrate that the Appellants had possession of the specific subject matter claimed, and the requirement for written description has been met.

In view of the foregoing arguments and legal authority, reversal of the rejections is requested.

Respectfully submitted,

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CLAIMS APPENDIX

1. A method of treating an inflamed orthopedic joint, said joint comprising i) opposing hyaline cartilage articular surfaces, ii) a peripheral collagenous capsule defining a central joint space and iii) synovial fluid contained within the joint space, comprising trans-capsularly administering into the joint space a formulation comprising an effective amount of an inhibitor of TNF-α synthesis such that the inflamed orthopedic joint is treated.

2. The method of claim 1, wherein the joint is a knee joint.

34. The method of claim 1, wherein the formulation further comprises at least one growth factor.

36. The method of claim 1, wherein the formulation further comprises a liposomal delivery system.

37. The method of claim 1, wherein the formulation is administered in an amount of less than 1 cc.

38. The method of claim 1, wherein the inhibitor of TNF-α synthesis is present in the formulation in an amount of at least 100 mg/ml.

39. The method of claim 1, wherein the formulation further comprises a sustained release device.

40. The method of claim 39, wherein the sustained release device comprises a hydrogel.

41. The method of claim 39, wherein the sustained release device provides controlled release.

42. The method of claim 39, wherein the sustained release device provides continuous release.

43. The method of claim 39, wherein the sustained release device provides intermittent release.

45. The method of claim 39, wherein the sustained release device comprises microspheres having a plurality of degradation rates.

46. The method of claim 39, wherein the sustained release device comprises an inflammatory-responsive delivery system.

47. The method of claim 1, wherein the formulation is provided closely adjacent to the outer wall of the capsule.

48. The method of claim 1, wherein the inhibitor of TNF-α synthesis is present in the formulation in a maximum amount of 0.5 mg.

49. The method of claim 1, wherein the formulation further comprises a growth factor present in an amount effective to repair joint tissue.

50. The method of claim 49, wherein the growth factor is provided by platelet concentrate.

51. The method of claim 1, wherein the inhibitor of TNF-α synthesis therapeutically inhibits the production of a cytokine.

53. The method of claim 1, wherein the formulation is injected into the synovial fluid.

54. The method of claim 1, wherein the formulation includes a viscosupplement.

55. The method of claim 1, wherein a portion of the synovial fluid is removed prior to administration of the inhibitor of TNF-α synthesis.

56. The method of claim 1, wherein the administration is performed through a needle.

57. The method of claim 1, wherein the formulation is administered through a drug pump.

58. The method of claim 1, wherein the formulation is administered in a volume of between 0.03 ml and 0.3 ml.

60. The method of claim 1, wherein the administration comprises providing the formulation in a patch attached to an outer wall of the capsule.

61. The method of claim 1, wherein the administration comprises providing the formulation in a depot at a location closely adjacent an outer wall of the capsule.

63. The method of claim 1, wherein the inhibitor of TNF-α synthesis is predominantly released from the formulation by diffusion of the high specificity antagonist through a sustained delivery device.

64. The method of claim 63, wherein the sustained delivery device is a polymer.

65. The method of claim 1, wherein the inhibitor of TNF-α synthesis is predominantly released from the formulation by biodegradation of a sustained delivery device.

EVIDENCE APPENDIX

1. Lehman *et al.*, "Thalidomide Therapy for Recalcitrant Systemic Onset Juvenile Rheumatoid Arthritis," *J. Pediatrics, 140*:125-127 (2002).

   Lehman *et al.* was listed by the Examiner as Reference V on form PTO-892 accompanying the Office Action dated January 4, 2006.

2. Dunn, EP 1 153607 A2, Publication Date: November 14, 2001.

   Dunn was listed by the Examiner as Reference N on form PTO-892 accompanying the Office Action dated January 4, 2006.

3. Pike *et al.*, US 2003/0134792, Publication Date: July 17, 2003.

   Pike *et al.* was listed by the Examiner as Reference A on form PTO-892 accompanying the Office Action dated January 4, 2006.

4. Molloy *et al.*, "*The* Roles of Growth Factors in Tendon and Ligament Healing," *Sports Med.*, 33:381-394 (2003).

   Molloy *et al.* was listed by the Examiner as Reference X on form PTO-892 accompanying the Office Action dated January 4, 2006.

5. Gori *et al.*, "Tumor Necrosis Factor-α Increased production During Thalidomide Treatment in Patients with Tuberculosis and Human Immunodeficiency Virus Coinfection," *J. Infect. Dis. 182*:639-640 (2000).

   Gori *et al.* was provided as Exhibit A with the Amendment entered into the record on April 4, 2006.

6. Smith *et al.*, US 2002/0169162, Publication Date: November 14, 2002.

   Smith *et al.* was listed by the Examiner as Reference B on form PTO-892 accompanying the Office Action dated January 4, 2006.

7. Cardone *et al.*,"Diagnostic and Therapeutic Injection of the Hip and Knee," *American Family Physician,* 67: 2147-2152 (2003).

   Cardone *et al.* was listed by the Examiner as Reference U on form PTO-892 accompanying the Office Action dated January 4, 2006.

8. LaVan, *et al.*, "Small-scale Systems for In Vivo Drug Delivery," *Nature Biotechnology 21*: 1184-1191 (2003).

   LaVan was listed by the Examiner Reference U on form PTO-892 accompanying the Office Action dated January 4, 2006.

9. Braun, J. and Sieper, J., "Overview of The Use of The Anti-TNF Agent Infliximab in Chronic Inflammatory Diseases," *Expert Opin. Biol. Ther. 3*(1):141-168 (2003).

   Braun, J. and Sieper, J. was listed by the Examiner Reference V on form PTO-892 accompanying the Office Action dated June 27, 2006.

RELATED PROCEEDINGS

NONE